REMARKS

Claims 1 to 19, 22, 25, 41, 42, and 52 to 73 are pending in the application. Claims 3, 52, and 54 have been amended, herein. No claims have been canceled, and no new claims have been added. Applicant respectfully requests reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Indefiniteness

Claims 3, 52, and 54 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the phrase "conventional antiviral compounds." The Office Action asserts that the meaning of the term "conventional" is unclear and inquires as to whether the term is intended as a claim limitation. Without conceding the correctness of the assertion, claims 3, 52, and 54 have been amended to replace the term "conventional" with the term "additional." In addition, claim 52 has been amended to replace the term "antiviral medicaments" with the term "antiviral compounds." Support for the amendments is found throughout the specification as originally filed, including, for example, paragraphs 117 and 118. No new matter has been added. The rejection has been obviated, and Applicant respectfully requests withdrawal thereof.

Alleged Lack of Enablement

Claims 1 to 19, 22, 25, 41, 42, and 52 to 73 have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Office Action asserts that the specification is enabling for methods of inhibiting or reducing HCV 1b replication in an individual infected with HCV, and having hepatocellular carcinoma or cells that do not express argininosuccinate synthase (ASS) and are auxotrophic for arginine, but does not enable methods of inhibiting or reducing HCV replication in an individual infected with HCV that does not suffer from hepatocellular carcinoma or does not have cells that do not express ASS and are auxotrophic for arginine. Applicants respectfully traverse the rejection because the specification enables those skilled in the art to make and use the full scope of the subject matter encompassed by the claims without undue experimentation.

The Examiner bears the burden of establishing a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). The Examiner must explain why he or she doubts the truth or accuracy of any statement in a supporting disclosure, and must support his or her assertions with acceptable evidence or reasoning. *In re Marzocchi*, 169 U.S.P.Q. 367, 360-70 (C.C.P.A. 1971).

The Examiner apparently doubts the validity of the data presented in the present specification because she bases her finding of lack of enablement on assertions that are contradicted by Applicant's data. The Examiner fails to explain why she doubts the accuracy Applicant's data, however. In addition, the Examiner fails to support her assertions of lack of enablement with acceptable evidence or reasoning.

As described in Example 8 of the specification, and as explained in the attached Declaration of John S. Bomalaski, arginine deiminase covalently bound to polyethylene glycol (ADI-PEG) inhibits the replication of Hepatitis C virus (HCV) *in vitro* through a mechanism that does not involve or require the killing of hepatocellular carcinoma (HCC) cells. Cultures of AVA5 cells were treated with various concentrations of ADI-PEG and the selectivity index was determined, which is an indicator of the level of inhibition of viral replication that occurs in the absence of the killing of host cells. A selectivity index of greater than 10 indicates that viral replication is selectively inhibited in the absence of host cell killing. As can be seen from the results presented in Example 8, ADI-PEG inhibits HCV replication with a selectivity index of 12, indicating that the enzyme inhibits HCV replication through a mechanism that does not involve the killing of host cells.

The Examiner asserts, however, that HCC cells are the primary site for HCV replication, and the inhibition of HCV replication observed by Applicant results from the killing of HCC cells by ADI-PEG. Although ADI has been shown to kill various HCC cell lines *in vitro* and *in vivo*[1], it does not necessarily follow, for a number of reasons, that ADI-PEG inhibits HCV replication by killing HCC cells. As an initial matter, as explained in the attached Declaration, HCV replication occurs diffusely throughout the liver and does not occur only in HCC cells, indicating that HCC cells are not required for HCV replication. In addition, most patients that have HCV do not have HCC, providing further evidence that

1 Reported, for example, at page 1816 of Izzo, F., *et al.*, *J. Clin. Oncol.*, 2004, 22, 1815-1822.

HCC cells are not required for HCV replication. Secondly, as discussed above, ADI-PEG has been shown to selectively inhibit HCV replication by a mechanism that is independent of the killing of host cells. Finally, the results of clinical trials conducted on behalf of Phoenix Pharmacologics, which are presented in Table III of the specification and explained in the attached Declaration, indicate that a correlation does not exist between the response of HCC tumors to ADI-PEG and the response of HCV to ADI-PEG. For example, in patient 1, HCC tumors were only modestly reduced by ADI-PEG, but ADI-PEG decreased the HCV titer by over 99 %. In patient 2, the HCC tumors were stable, indicating that they were not affected by ADI-PEG, but the HCV titers decreased 96 % after ADI-PEG treatment. Patient 6 made a complete recovery from HCC with ADI-PEG treatment, but the patient's HCV titers only decreased 47 %. In patient 12, ADI-PEG modestly reduced HCC tumors, while the patient's HCV titers actually increased. The lack of correlation between the response of HCC tumors and HCV viral titers to ADI-PEG provides further evidence that HCV replication is inhibited by ADI-PEG through a mechanism that does not depend upon the killing of HCC cells.

Accordingly, it would be incorrect to ignore the data presented in the specification and to conclude, as the Examiner has done, that because ADI has been reported in the literature to kill HCC cells *in vitro* and *in vivo*, ADI-PEG inhibits HCV replication by killing HCC cells. The specification demonstrates that HCV replication is selectively inhibited by ADI-PEG through a mechanism that does not involve the killing of HCC cells. The Examiner has not explained why she doubts the validity of Applicant's data, and, accordingly, fails to support her assertions of lack of enablement with valid evidence or reasoning.

The Examiner also asserts that the specification does not enable methods for inhibiting the replication of all genotypes of HCV with ADI-PEG, and maintains that the data presented in Table 3 of the specification support her assertion. Table 3 presents the results of clinical trials in which patients chronically infected with HCV and suffering from HCC were treated with ADI-PEG. The table indicates that the viral titers of patients infected with HCV serotype 2c actually increased after ADI-PEG treatment. The results of more recent clinical trials indicate, however, that ADI-PEG significantly reduces HCV titers in patients infected with HCV of differing serotypes, including serotype 2a/2c. As explained in the attached Declaration, patients suffering from HCC and infected with HCV of various serotypes were

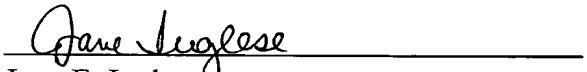
administered ADI-PEG. In four of twelve patients the HCV titers decreased over 99 % following ADI-PEG treatment. Two of the four patients were infected with HCV serotype 1b and the remaining two patients were infected with HCV serotype 2a/2c. ADI-PEG thus effectively inhibits the replication of HCV serotype 1b, as well as serotype 2a/2c. The specification thus enables methods for inhibiting the replication of HCV of various serotypes using ADI-PEG, and, therefore, enables those skilled in the art to practice the full scope of the subject matter defined by the claims without undue experimentation. Applicant, accordingly, respectfully requests withdrawal of the rejection.

Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully Submitted,

Date: August 22, 2005



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